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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,521	12/05/2003	Atul Varadhachary	HO-P02703US2	8270

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FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,521	VARADHACHARY ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 26-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 26-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/04;2/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-20 and 26-40 in the response filed November 17, 2004 is acknowledged. Therefore, claims 1-20 and 26-40 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 7-20, 27 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 1, 7-20 and 32 are indefinite because of the use of the term "improvement". The cited term renders the claim indefinite, it is unclear what the improvement is in the claimed method. Claims 7-20 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

4. Claim 13 is indefinite because the claim recites the term "said N-terminal lactoferrin variant comprises at least 1% to at least 50% of the lactoferrin composition", while claim 11, from which claim 13 depends from, cites "said lactoferrin composition comprises an N-terminal lactoferrin variant", it is not clear how the N-terminal lactoferrin variant, which is a peptide, can comprise a portion (1-50%) of the lactoferrin composition, and whether the percentage is "weight by volume" or "weight by weight"?

5. Claim 27 is indefinite because the claim lacks an essential step in the method of enhancing a mucosal immune response. The missing step is the outcome of the treatment, it is not clear what is the endpoint of the process.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-9, 15, 17, 20, 26-32 and 34-40 are rejected under 35 U.S.C. 102(b) as anticipated by Kruzel *et al.* (International Congress Series (2000), 1195 (Lactoferrin, Structure, Function and Applications), 301-310).

Kruzel *et al.* disclose insult-induced acute inflammation is followed by repair processes including negative feedback under normal physiological condition, however, if not controlled, the acute inflammation may develop into fast-progressing systemic inflammatory response syndrome (SIRS) such as sepsis, septic shock and multiple organ failure (page 302); and human lactoferrin is given orally by gavage in maintaining immune homeostasis in two in vivo models, LPS-induced endotoxemic mice and healthy human individuals (page 304, last paragraph; claims 7-9, 17 and 20). Naive mice were injected with lethal doses of LPS and was then treated with lactoferrin orally (2.5 mg; claim 15) three times, and it was found the intestinal injury was reduced and lactoferrin attenuates the toxic effect of LPS by maintaining the mucosal integrity (page 305; claims 5, 27, 36). Although Kruzel *et al.* do not specifically indicates lactoferrin stimulates IL-18 in the gastrointestinal tract and reduces the production or activity of

inflammatory cytokines, the reference indicates the administration of lactoferrin by gavage maintains immune homeostasis, thus lactoferrin would produce these activities in the gastrointestinal tract (claims 28-30, 39-40). The reference also teaches lactoferrin (7.5 mg/mouse) orally administered before the LPS injection improved the mortality rate of mice as compared with saline controls (pages 305-306; claims 1-4, 6, 26, 31, 32, 34, 35, 37 and 38).

7. Claims 1-10, 15, 17, 20, 26, 27 and 31-38 are rejected under 35 U.S.C. 102(b) as anticipated by Edde *et al.* (Am. J. Physiol. Gastrointest. Liver Physiol. 281, G1140-G1150, November 2001).

Edde *et al.* teach neonatal rats pretreated orally with recombinant human lactoferrin (rh-LF) has less bacteremia, lower disease severity scores and lower death rates after intestinal infection with *Escherichia coli* (Fig. 1) and the number of E. coli cultured from blood and liver were significantly lower in the animals pretreated with either rh-LF or rh-LF + $FeSO_4$ compared with either NaCl-treated or NaCl + $FeSO_4$ treated pups (Fig. 2; pages G1143-G1144; claims 1-6, 8-10, 26, 27 and 31-38), where the treatment groups received either rh-LF (350 $mg.kg^{-1}.day^{-1}$; corresponding to 1.75 $mg.kg^{-1}.day^{-1}$ for neonatal rats weighing 10 g; claim 15) or rh-LF + $FeSO_4$ instilled into stomach (0.4 ml/pup; claim 7, 17, 20).

8. Claims 1-10, 15-20, 26-32 and 34-40 are rejected under 35 U.S.C. 102(e) as anticipated by Kruzel *et al.* (US 2001/0056067, filed October 29, 1999).

Kruzel *et al.* teach the effectiveness of lactoferrin in the treatment or prevention of insult-induced metabolic imbalance in a mouse model of LPS endotoxemia, injection of LPS at excessive levels to exemplify the effect of lactoferrin under acute conditions such as sepsis or multiple organ failure or at lower levels to illustrate the effect of lactoferrin on stress or trauma

in mice (paragraph [0031]), e.g., native mice were gavaged with saline solution of bovine lactoferrin (7.5 mg/dose; claims 7, 15, 17, 20) prior or after the LPS injection significantly increased the survival of mice (Example 5; claim 1-4, 6, 26, 31, 32, 34, 35, 37 and 38); naive mice were injected with lethal doses of LPS and was then treated with saline solution of lactoferrin by gavaging (100 μl of 10 mg/ml) three times, and lactoferrin maintains the physiological function of gut during LPS-induced metabolic imbalance (Example 7; claims 5, 27, 36). Although Kruzel *et al.* do not specifically indicates lactoferrin stimulates IL-18 in the gastrointestinal tract and reduces the production or activity of inflammatory cytokines, the reference indicates the administration of lactoferrin by gavage maintains the physiological function of gut, thus lactoferrin would produce these activities in the gastrointestinal tract (claims 28-30, 39-40). The lactoferrin can be human lactoferrin or recombinantly produced (paragraphs [0028] and [0029]; claims 8-10); and lactoferrin can be administered enterally, preferably orally in the form of a powder, solution or gel, and the daily dose for in treating animals is 0.1 to 20 mg (paragraph [0030]; claims 15-19).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 2, 7-12 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Van Bree *et al.* (WO 01/72322, October 4, 2001).

Van Bree *et al.* teach human lactoferrin (hLF) can block free LPS and cause them to clear from the body more rapidly, and mask their inflammatory activity; hLF or LF variants (e.g., N-terminal variants, hLF(1-11), hLF(2-11) and hLF(3-11); page 27; claims 11 and 12), which have the biological activities of natural LF, at effective dose (e.g., 10-100 mg of hLF; claims 15 and 16) can be used to treat large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection (pages 3-4; page 20, lines 24-29; page 24; claims 1, 2, 8, 9). The lactoferrin variants can be produced by proteolytic cleavage of LF or recombinant technique (pages 11-13; claim 10); and lactoferrin can be administered orally in the form of a solid or solution, and the active components can be encapsulated in gelatin capsules together with inactive ingredients and carriers such as glucose, mannitol or magnesium carbonate (an antacid), and the formulated solid or liquid formulations can be in an enteric-coated form (page 26; claims 7, 17-19). Although the reference does not provide a specific example for a method of treating bacteremia using a lactoferrin composition containing the N-terminal variant, the reference indicates a high dose of hLF can be administered in the treatment, and the LF variant which has the biological activity of natural LF can also be used, thus at the time of invention was made, it would have been obvious to one of ordinary skill in the art to use LF or its N-terminal

variant in the method of treating bacteremia, which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
January 6, 2005